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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,016	10/04/2001	Tariq M. Rana	267/302	2378
23869	7590	11/24/2004	EXAMINER	
HOFFMANN & BARON, LLP 6900 JERICHO TURNPIKE SYOSSET, NY 11791			LUKTON, DAVID	
			ART UNIT	PAPER NUMBER
			1653	

DATE MAILED: 11/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/972,016	RANA ET AL.	
Examiner	Art Unit	
David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 10 September 2004.
2a) This action is **FINAL**. 2b) This action is non-final.
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-14 and 16-34 is/are pending in the application.
4a) Of the above claim(s) 1-14 and 19-27 is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 16-18 and 28-34 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____.

Pursuant to the directives of the response filed 9/10/04, claims 16-17 have been amended, claim 15 cancelled, and claims 28-34 added. Claims 1-14, 16-34 are now pending. Claims 1-14 and 19-27 remain withdrawn from consideration; claims 16-18 and 28-34 are examined in this Office action.

Applicants' arguments filed 9/10/04 have been considered and found not persuasive.

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The specification is objected to. On page 1, paragraph 2, there is a priority claim to application 06/237,881. However, this application was filed in February of 1981, and pertains to an inflatable balloon distress marker. It appears that provisional application 60/237,881 may be intended instead.

◆

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-18 and 28-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention.

In the specification as filed, the (elected) invention that is described requires that both of the following conditions be met: (a) the protein is labeled with a donor dye molecule, and (b) the RNA is labeled with an acceptor dye molecule. Descriptive support for this is evident on page 10, paragraph 0026, and in (original) claim 15. Consider what claim 28 now recites. Claim 28 recites that the protein is labeled with a “first fluorescent dye molecule”, and that the RNA is labeled with a “second fluorescent dye molecule”. Accordingly, claim 28 encompasses both of the following two possibilities:

- (i) the protein is labeled with a donor fluorescent dye molecule, and concomitantly the RNA is labeled with an acceptor fluorescent dye molecule; and
- (ii) the protein is labeled with a acceptor fluorescent dye molecule, and concomitantly the RNA is labeled with a donor fluorescent dye molecule.

This ground of rejection is directed at the second of these two possibilities. There is no statement or suggestion anywhere in the specification that protein/RNA “interactions” can be determined when the protein is labeled with an “acceptor” fluorophore, while at the same time the RNA is labeled with a “donor” fluorophore.

Applicants have asserted (page 10, response) that “useful information” can be obtained if the protein is labeled with the acceptor fluorophore, and the RNA with the donor. Perhaps that is true, and perhaps not, but that is not the issue here. The issue is also not

whether the skilled spectroscopist would be able to create his own experiments in which a protein is labeled with an "acceptor" fluorophore, and an RNA molecule is labeled with a "donor" fluorophore. The issue instead is whether such a combination is described in the application to begin with, and if it is, whether the specification explains how to determine a protein/RNA "interaction" for such a combination. If applicants believe that such description exists, applicants should point out the page number and paragraph number.



Claims 16-18 and 28-34 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 28 recites that one can determine the proximity between the protein and the RNA molecule. The examiner will stipulate that the skilled artisan would be able to determine the distance between two fluorophores. But that is not what the claim states. The claim recites that one can determine the "molecular proximity" between the entire protein molecule and the entire RNA molecule. However, as applicants may be aware, proteins do not exist simply as spheres. The same is true of polynucleotides. Any of several shapes is possible for the two molecules to begin with, and when the two are in close proximity, one molecule can easily "wrap around" the

other. Thus, at a given point along the protein sequence, a given amino acid might be no closer than 300 Angstroms to the nearest ribonucleotide unit. At another point, there may be just 10 Angstroms separating the two. Thus, to speak of the entire molecule is not meaningful. And more to the point, the specification does not teach the skilled artisan how to determine the "proximity" between the entire protein molecule and the entire RNA molecule. What may be intended is simply to determine a distance between the two fluorophores.

Another issue concerns claim 30. This claim suggests that one can determine the degree of binding between a protein and an RNA molecule. However, the specification provides no guidance as to how to do this. An important point to be made is that distance, even a "close" distance between two molecules does not equate with binding. The term "binding", in a biochemical context, generally refers to an equilibrium between two molecules that are in close association versus the two molecules which are dissociated. A dissociation constant ("K_d") is often used to quantitate this equilibrium. However, ~~however~~ the specification does not teach the skilled artisan how to determine any such dissociation constant by making a single determination of interprobe distances. As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of

experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Based on the record thus far, it is evident that the prior art does not remedy the deficiencies in the specification. Accordingly, "undue experimentation" would be required to determine a K_d by making a determination of interprobe distance.

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Claims 15 and 29 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 15 recites (last line) the phrase "determining distance-dependent interaction". The meaning of this is unclear. The term "interaction" could refer to any of a number of chemical or physical phenomena. Is the "interaction" one of attraction or repulsion? Does the phrase at issue refer to a distance measurement of some kind? How does one draw an inference as to the nature of the interaction?
- In claim 29, line 2, it appears that the term *fluorescence energy transfer* may be intended, rather than just "fluorescence energy".

◆

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 16, 18, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Karn (USP 6,316,194).

Karn discloses methods of assessing the interaction between antimicrobial compounds and RNA using FRET. Among the antimicrobial compounds are various peptides and proteins. Also disclosed (table 6, col 28) are various donor/acceptor pairs for FRET. Also disclosed (col 13, line 55+) that the donor can be attached to the RNA, and the acceptor to the antimicrobial, or vice versa; i.e., the implication is that either approach will provide useful information. The fluorescence spectroscopist of ordinary skill would have been motivated to use one of the donor/acceptor pairs listed to study interactions between antimicrobial

peptides, and RNA.

In response to the foregoing, applicants have argued that Karn does not disclose attachment of the fluorophore to the protein after synthesis of the protein. Applicants then state the following:

"In the '194 patent, amino acid analogs are first labeled with structural probes and then the labeled amino acid analogs are used in the solid phase peptide synthesis to produce the labeled site-specific modified protein. Therefore, in these references, the labeling occurs during the synthesis of the site-specific modified protein".

Where such a teaching might be found in the '194 patent is not disclosed by applicants.

(In the event that applicants wish to reaffirm this alleged teaching, applicants are requested to point out the column number and line number). As it happens, synthesis of the protein is not required to practice the invention of Karn ('194). The matter of attachment of fluorophores is discussed, e.g., at col 12. Karn discloses that the fluorophore can be attached to a ketone moiety or to an aldehyde moiety or to a dehydroalanine moiety. A protein which contains any one of these groups qualifies as a "modified protein". But even if Karn had only suggested reacting an isothiocyanate derivative of a fluorophore with a lysine *epsilon* amino group, the claims would still be rendered obvious. As it happens, if a protein chemist is presented with the sequence of a given protein, there will exist at least one "site specific modified protein" that will be rendered obvious thereby. The reason is that if one takes a "first" protein that contains a

particular amino acid at a given position, and modifies that amino acid to introduce a single methylene group, the result will be a "second" protein that the skilled protein chemist would expect, *a priori*, to exhibit substantially identical activity and physical properties as the "first" protein. Examples of such substitutions would be ethylglycine for alanine, or phenethylglycine for phenylalanine, or hydroxyethylglycine for serine. It is recognized that compounds that are close homologs, differing by just one methylene group usually exhibit the same activity. [*In re Shetty* (195 USPQ 753) and *In re Hass & Susie* (60 USPQ 544)]. Claim 28 imposes no structural limitations on the "analog" of the amino acid. Clearly then, adding or subtracting a single methylene group from an amino acid would generate an "analog". The claims do not actually require that the chemist undertakes a synthetic procedure which would give rise to the "modified protein"; the claims require only that the "modified protein" be provided. Suppose, for example, that the protein chemist of ordinary skill were presented with the following sequence (arbitrarily selected), wherein "X" represents alanine:

QWERTSVPQYMKNCXVKESDFTILKHCVNMETYWEEQR

The protein chemist of ordinary skill would immediately recognize that the protein in which "X" is ethylglycine will exhibit substantially identical activity and physical properties as the protein in which "X" is alanine. At the same time, he will recognize that ethylglycine qualifies as an amino acid "analog". Thus, as indicated above, if a

protein chemist is presented with the sequence of a given protein, there will exist at least one "site specific modified protein" that will be rendered obvious thereby.

Applicants' recitation of the phrase "labeling ...post-synthetically" (page 9, response), while not "wrong" in all cases, is moot in the instant case. As indicated above, the claims do not require that a modified protein be synthesized, only that it be "provided".

Thus, the protein chemist of ordinary skill would find it obvious, based on the teachings of Karn, that a "modified" protein can be provided. Moreover, as indicated above, proteins which contain a ketone moiety or an aldehyde moiety or a dehydroalanine moiety all qualify as a "modified protein".

Thus, the claims are rendered obvious.



Claims 16, 18, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Karn (USP 6,573,045).

Karn discloses methods of assessing RNA/peptide interactions by FRET. Various donor/acceptor pairs are listed in table 2 (col 40). In various experiments, RNA was labeled with DABCYL, and the peptide was labeled with rhodamine. (see, e.g., col 35, line 60+; col 37, line 20+; col 37, line 50+). In this particular configuration, rhodamine is the donor, and DABCYL is the acceptor. The rhodamine/fluorescein pair is also disclosed (e.g., table 2, col 40).

In response to the foregoing, applicants have argued that Karn does not disclose attachment

of the fluorophore to the protein after synthesis of the protein. Applicants then state the following:

"In the '194 patent, amino acid analogs are first labeled with structural probes and then the labeled amino acid analogs are used in the solid phase peptide synthesis to produce the labeled site-specific modified protein. Therefore, in these references, the labeling occurs during the synthesis of the site-specific modified protein".

However, it is not apparent where in the patent such a teaching might be found. Consider the information provided at col 28, line 34+, where preparation of the following peptide is described:

FAM-Phe-Thr-Thr-Lys-Ala-Leu-Gly-Ile-Ser-Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Pro-Pro-Gln-Gly-Ser-Gln-Thr-His-Gln-Val-Ser-Leu-Ser-Lys-Gln

The implication is that the "FAM" group was attached to the N-terminus of the peptide while the protecting groups were still present on the side chains; otherwise one would expect reaction at the lysine *epsilon* amino groups. The first point is that when protecting groups are present on the side chains of amino acids, the resulting protein qualifies as a "site specific modified protein". The analysis could stop there and be sufficient. In addition, however, there is the matter of the one-carbon homologs discussed above (the §103 over Karn ('194). Thus, given the peptide indicated above, the following peptide is rendered obvious ("Xaa" represents ethylglycine):

Phe-Thr-Thr-Lys-Xaa-Leu-Gly-Ile-Ser-Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Pro-Pro-Gln-Gly-Ser-Gln-Thr-His-Gln-Val-Ser-Leu-Ser-Lys-Gln

If one then treats this peptide with FAM succinimidyl ester, the result will be process in which a "modified protein" has been "provided", and a fluorescent dye molecule is subsequently labeled thereon. Contrary to what applicants have asserted (page 9, response), the "post-synthetic labeling" is not a requirement of the claims, but even if it were, this condition is met by the reference. Applicants have also argued that a disadvantage of the "prior art approach" is that once the "labeled analog" is introduced into a protein, the specified site is no longer available for modification with other labels. First, the claims do not require that a given site be available for modification with other labels. And second, the claims impose no limitations on the initial site of labeling.

Accordingly, the rejection is maintained.



Claims 16, 18, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Zhang (*J. Biol. Chem.* **275**, 34314, 2000).

As indicated previously, Zhang discloses a study of the interactions between TAR RNA and a tat peptide, using FRET. Fluorescein was bonded to the RNA, and rhodamine to the peptide.

In response, applicants have argued that Zhang does not disclose replacement of an amino acid with an amino acid analog. However, as indicated above, the protein chemist of ordinary skill would have recognized the benignity of this structural change. [*In re Shetty* (195 USPQ 753) and *In re Hass & Susie* (60 USPQ 544)]. Applicants have also

argued that structural alterations at lysines are precluded by the claims. However, this ground of rejection does not require a structural alteration at a lysine. A homolog of almost any amino acid (other than lysine or cysteine) would meet the requirements of the claims.

The rejection is maintained.

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Claims 16, 28-31 are rejected under 35 U.S.C. §103 as being unpatentable over Czworkowski J (*Biochemistry* **30** (19) 4821-30, 1991) or Odom O. W. (*Biochemistry* **29** (48) 10734-44, 1990) or Odom O. W. (*Biochemistry* **23**, 5069, 1984).

Each of Czworkowski (1991), Odom (1990) and Odom (1984) describe experiments in which RNA and a protein are both labeled with a fluorophore, and the extent of fluorescence energy transfer between the two probes is determined. None of the references discloses that the ribosomal protein is “site specific[ally] modified”. However, the protein chemist of ordinary skill would recognize that extending a side chain by a single methylene group would not adversely affect the function or activity of the ribosomal protein. [*In re Shetty* (195 USPQ 753) and *In re Hass & Susie* (60 USPQ 544)].

Thus, the claims are rendered obvious.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1300